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Original Scientific Paper

Exercise training increases oxygen uptake efficiency slope in chronic heart failure

Maaike G.J. Gademan[a], Cees A. Swenne[a], Harriette F. Verwey[a], Hedde van de Vooren[a], Joris C.W. Haest[a], Henk J. van Exel[a,b], Caroline M.H.B. Lucas[c], Ger V.J. Cleuren[c], Martin J. Schalij[a] and Ernst E. van der Wall[a]

[a]Department of Cardiology, Leiden University Medical Center, [b]Department of Cardiopulmonary Rehabilitation, Rijnland Rehabilitation Center, Leiden and [c]Heart Failure Outpatient Clinic, Rijnland Hospital, Leiderdorp, The Netherlands

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Background and aim **The oxygen uptake efficiency slope (OUES) is a novel measure of cardiopulmonary reserve. OUES is measured during an exercise test, but it is independent of the maximally achieved exercise intensity. It has a higher prognostic value in chronic heart failure (CHF) than other exercise test-derived variables such as $\dot{V}_{O_{2peak}}$ or $\dot{V}E/\dot{V}_{CO_2}$ slope. Exercise training improves $\dot{V}_{O_{2peak}}$ and $\dot{V}E/\dot{V}_{CO_2}$ in CHF patients. We hypothesized that exercise training also improves OUES.**

Methods and results **We studied 34 New York Heart Association (NYHA) class II–III CHF patients who constituted an exercise training group T ($N=20$; 19 men/1 woman; age 60±9 years; left ventricular ejection fraction 34±5%) and a control group C ($N=14$; 13 men/one woman; age 63±10 years; left ventricular ejection fraction 34±7%). A symptom-limited exercise test was performed at baseline and repeated after 4 weeks (C) or after completion of the training program (T). Exercise training increased NYHA class from 2.6 to 2.0 ($P<0.05$), $\dot{V}_{O_{2peak}}$ by 14% [P(TvsC)<0.01], and OUES by 19% [P(TvsC)<0.01]. Exercise training decreased $\dot{V}E/\dot{V}_{CO_2}$ by 14% [P(TvsC)<0.05].**

Conclusion **Exercise training improved NYHA class, $\dot{V}_{O_{2peak}}$, $\dot{V}E/\dot{V}_{CO_2}$ and also OUES. This finding is of great potential interest as OUES is insensitive for peak load. Follow-up studies are needed to demonstrate whether OUES improvements induced by exercise training are associated with improved prognosis.** ***Eur J Cardiovasc Prev Rehabil*** **15:140–144 © 2008 The European Society of Cardiology**

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Introduction

Cardiopulmonary performance is often assessed by maximal oxygen uptake ($\dot{V}_{O_{2\,max}}$). Basically, $\dot{V}_{O_{2\,max}}$ is an objective parameter, that is defined as the point at which oxygen uptake reaches a plateau despite continuing exercise and increasing workload [1]. Unfortunately, such a plateau is often difficult to perceive [2], and in symptom-limited exercise tests, as performed in chronic heart failure (CHF), the plateau is often not attained [3]. Hence, in practice, peak oxygen uptake ($\dot{V}_{O_{2peak}}$) is assessed in CHF patients instead of $\dot{V}_{O_{2\,max}}$ [4]. Obviously peak oxygen uptake is strongly influenced by the motivation of the patient, the selected exercise protocol and the tester's subjective choice of the test end point [5,6].

As a result of these drawbacks, Baba *et al.* [7] have introduced the oxygen uptake efficiency slope (OUES), an objective and reproducible measure of cardiopulmonary function reserve that can also be measured with submaximal exercise [8–10]. In CHF patients, it was shown that among other exercise test-derived parameters (peak oxygen uptake –$\dot{V}_{O_{2peak}}$–; ventilatory response to exercise –$\dot{V}E/\dot{V}_{CO_2}$ slope–; ventilatory anaerobic

Correspondence to Cees A. Swenne, PhD, Department of Cardiology, Leiden University Medical Center, PO Box 9600, 2300 RC Leiden, The Netherlands
Tel: +31 71 526 1972; fax: +31 84 221 8904; e-mail: c.a.swenne@lumc.nl

threshold –VAT–) OUES had the strongest prognostic value; OUES was also the only parameter with independent prognostic value [11]. It is known that exercise training improves $\dot{V}_{O_{2peak}}$ and $\dot{V}E/\dot{V}_{CO_2}$ in CHF patients [12–14], however, convincing proof that exercise training also increases OUES in CHF patients has not been published yet. There certainly are positive indicators that this might be the case: exercise training improves OUES in other patient groups (coronary artery disease, hemodialysis [15,16]), and Van Laethem *et al.* [17] recently published, in an uncontrolled study, suggestive evidence that exercise training also increases OUES in CHF patients. Our current study aims to complete this evidence by using a controlled protocol.

Methods

Patients

The Medical Ethics Committees of the Leiden University Medical Centre and of the Rijnland Rehabilitation Center approved the protocol of this study. The investigation conforms to the principles outlined in the Declaration of Helsinki [18]. All participants gave written informed consent. Eligible patients had CHF New York Heart Association (NYHA) class II or III, with systolic dysfunction and a left ventricular ejection fraction (LVEF) less than 45%. Patients with pulmonary hypertension and chronic obstructive pulmonary disease were excluded from the study.

Two groups of patients, a sedentary control group and an exercise training group, were defined as follows. Consecutive CHF patients who had one regular baseline symptom-limited exercise test before commencing their actual rehabilitation program, and in whom a final evaluative symptom-limited exercise test was performed 1 day after completing the last training session, constituted the training group. After inclusion of the exercise training group, we started inclusion of the control group. For this group, consecutive patients eligible for rehabilitation were selected who matched one of the participants of the training group for age (within 5 years), NYHA class (identical), LVEF (within 5%) and etiology (identical). The patients in the control group had two baseline symptom-limited exercise tests, 4 weeks apart, before starting their actual rehabilitation program. Table 1 summarizes the main patient characteristics of the training and control groups.

Symptom-limited exercise testing

Symptom-limited exercise tests at baseline and after 4 weeks (control group) or after completion of the rehabilitation program (training group) were carried out with respiratory gas exchange analysis (Oxycon Pro, Jaeger-Viasys Healthcare, Hoechberg, Germany). Exercise intensity started at 5 W and was increased by 5 W every 30 s. Participants exercised to their self-determined maximal capacity or until the supervising physician stopped the test because of significant symptoms, such as chest pain, dizziness, potentially dangerous arrhythmias or ST-segment deviations, or marked systolic hypotension or hypertension. Breath-by-breath respiratory gas analyses were performed throughout the entire test. $\dot{V}_{O_2}$ values were determined over every 30-s period, and over the terminating measurement period at peak exercise when this was more than 15 s long. The last valid $\dot{V}_{O_2}$ value was taken as $\dot{V}_{O_{2peak}}$.

$\dot{V}E/\dot{V}_{CO_2}$ slope and oxygen uptake efficiency slope calculation

$\dot{V}E/\dot{V}_{CO_2}$ slope was obtained by linear regression analyses of the relation between $\dot{V}E$ and $\dot{V}_{O_2}$ during the entire symptom-limited exercise test.

OUES was computed by a linear least squares regression from the oxygen uptake on the logarithm of the minute ventilation ($\dot{V}E$) according to the following equation: $\dot{V}O_2 = a \cdot \log_{10} \dot{V}E + b$ [7]. Constant '*a*' is called the OUES, as it represents the rate of increase in oxygen uptake in response to a change in minute ventilation [7].

To assess the validity of OUES during a submaximal exercise test, OUES was also calculated from data derived form the first 75% (OUES75) and 90% (OUES90) of the entire exercise duration.

To compare the OUES results from our study group with reference values, we computed the predicted OUES for age, body surface area (BSA) and sex-matched normal participants according to the equations published by Hollenberg *et al.* [9]: for women, OUES = 1175–15.8 * age + 841 * BSA; for men, OUES = 1320–26.7 * age + 1394 * BSA.

Exercise training

Patients in the training group attended 30 exercise training sessions. Training sessions were conducted 2–3 times a week, lasted about 75 min and consisted of 20-min cycling, starting at 50% of the maximal load attained during the baseline symptom-limited exercise test, preceded/followed by warming up/cooling down. Per session, this load was increased, until the attained heart rate was equal to the heart rate at the anaerobic threshold as estimated during the baseline test. Further endurance exercise during 15 min was *ad libitum* and consisted of rowing or walking. Additionally, all patients in the training group conducted light resistance training, consisting of one series of 25 repetitions of each of the following exercises; flies, rowing, chest press, shoulder press, leg extension, leg curl, leg press and pull down. Intensity was chosen and, in the course of the training program, adjusted in such a way that the patient experienced nearly complete exhaustion of the involved muscle group after 25 repetitions.

Statistics

The statistical data are expressed as mean ± SD. Baseline characteristics were evaluated by using Mann–Whitney *U*-test and χ^2 tests, Yates correction was used. A Mann–Whitney *U*-test was used to compare, between the training and the control group, baseline values and individual changes in $\dot{V}_{O_{2peak}}$, $\dot{V}E/\dot{V}_{CO_2}$, OUES/kg, OUES, OUES90 and OUES75. A paired Student's *t*-test was used to compare the measured OUES with the reference OUES. NYHA functional class within the training group changes was evaluated with a Wilcoxon signed-rank test. Differences in OUES75, OUES90 and OUES of the entire maximal exercise duration were assessed by a repeated-measures analysis of variance.

Table 1 Patient characteristics

	Training group	Control group	*P* value
Sex	19M/1F	13M/1F	NS
Age (years)	60 ± 9	63 ± 10	NS
LVEF (%)	34 ± 5	34 ± 7	NS
BMI (kg/m^2)	27.3 ± 3.5	28.7 ± 3.0	NS
NYHA class	2.6 ± 0.5	2.3 ± 0.4	NS
Etiology			
Ischemic	11 (55%)	6 (43%)	NS
Nonischemic	9 (45%)	7 (57%)	NS
Medication			
Antithrombotic therapy	16 (80%)	11 (79%)	NS
ACE inhibitor/AII blocker	18 (90%)	14 (100%)	NS
Diuretic	12 (60%)	10 (71%)	NS
Spironolactone	3 (15%)	4 (29%)	NS
Beta-blocker	17 (85%)	12 (86%)	NS
Statin	14 (70%)	10 (71%)	NS
Digoxin	0 (0%)	0 (0%)	NS
Amiodarone	4 (20%)	1 (7%)	NS

BMI, body mass index (kg/m^2); F, female; LVEF, left ventricular ejection fraction; M, male; NS, not significant ($P>0.05$); NYHA, New York Heart Association functional class.

Results

Patient characteristics

No significant differences were found for sex, age, LVEF, body mass index, NYHA functional class, etiology and medication of the training and the control group (Table 1). Throughout the study, the type and dose of medications remained the same for all patients.

Oxygen consumption

Baseline $\dot{V}_{O_{2peak}}$ values of the training and the control groups did not differ significantly; exercise training increased $\dot{V}_{O_{2peak}}$ by 14%, this was significantly different ($P < 0.01$) from the change in the control group (Table 2).

$\dot{V}E/\dot{V}_{CO_2}$ slope

As expected, the $\dot{V}E/\dot{V}_{CO_2}$ slope was elevated, both groups exceeded the upper normal limit of 30 [19] (Table 2). Baseline $\dot{V}E/\dot{V}_{CO_2}$ slope values of the training and the control groups did not differ significantly; exercise training decreased $\dot{V}E/\dot{V}_{CO_2}$ slope by 14%. This difference was significant ($P < 0.01$) compared with the insignificant change in the control group (Table 2).

Oxygen uptake efficiency

Baseline OUES and OUES/kg values of the training and the control groups did not differ significantly; exercise training increased OUES by 19%, and OUES/kg by 17% (Table 2). This increase differed significantly ($P < 0.001$) from the change in the control group (Table 2).

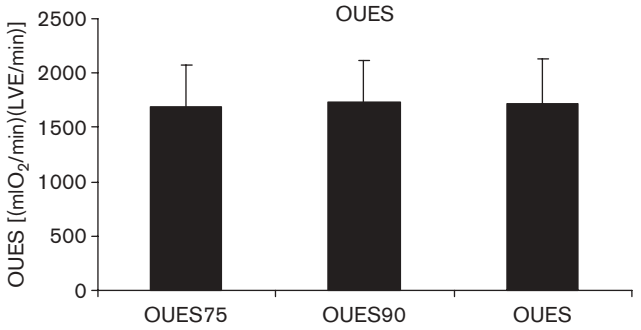
As expected, OUES75 and OUES90 did not differ relevantly from OUES (Fig. 1), OUES75 underestimated OUES by 1.4%, and OUES90 overestimated OUES by 0.5%. As there was no significant difference in the beginning in the analysis of variance repeated measures

Table 2 Changes in $\dot{V}_{O_{2peak}}$ and OUES

	Group	Baseline	Remeasurement	Change (%)	P_{BvsR}
OUES/kg [(mlO_2/min)/(L VE/min)]	Control	20.2 ± 4.7	21.2 ± 5.7	5	NS
	Training	19.8 ± 5.1	23.2 ± 4.8	17	<0.001
P_{CvsT}		NS	<0.001*		
OUES [(mlO_2/min)/(L VE/min)]	Control	1763 ± 362	1854 ± 451	5	NS
	Training	1690 ± 447	2017 ± 462	19	<0.001
P_{CvsT}		NS	<0.001*		
OUES90 [(mlO_2/min)/(L VE/min)]	Control	1792 ± 335	1903 ± 443	6	NS
	Training	1660 ± 470	2030 ± 436	22	<0.001
P_{CvsT}		NS	<0.001*		
OUES75 [(mlO_2/min)/(L VE/min)]	Control	1797 ± 324	1923 ± 440	7	NS
	Training	1609 ± 388	2010 ± 406	21	<0.001
P_{CvsT}		NS	<0.001*		
VE/V_{CO_2} slope	Control	35.5 ± 3.6	35.8 ± 3.9	0	NS
	Training	35.8 ± 9.6	31.0 ± 6.1	14	<0.01
P_{CvsT}		NS	<0.05*		
$\dot{V}_{O_{2peak}}$ (mlO_2/kg/min)	Control	17.1 ± 3.5	16.9 ± 3.9	−1	NS
	Training	16.9 ± 4.4	19.4 ± 4.9	14	<0.01
P_{CvsT}		NS	<0.01*		

$\dot{V}_{O_{2peak}}$, peak oxygen uptake (ml O_2/kg/min); BvsR, baseline vs. remeasurement; CvsT, control group vs. training group; NA, not applicable, NS, not significant; OUES, oxygen uptake efficiency slope (constant 'a' in equation $\dot{V}O_2 = a \cdot \log \dot{V}E + b$); OUES75, OUES calculated from data derived form the first 90% of the symptom limited exercise test; OUES90, OUES calculated from data derived form the first 90% of the symptom-limited exercise test. *P values for the difference between the change in parameters.

Fig. 1



Effect of shortened exercise duration on OUES. Effect of shortened exercise duration on OUES. OUES90: OUES calculated from data derived form the first 90% of the symptom limited exercise test; OUES75: OUES calculated from data derived form the first 75% of the symptom limited exercise test. OUES, oxygen uptake efficiency slope.

Table 3 Assessed versus predicted OUES

Group	Assessed OUES [(ml O_2/min)/(L VE/min)]	Predicted OUES [(ml O_2/min)/(L VE/min)]	% predicted OUES [(ml O_2/min)/(L VE/min)]	$P_{\text{assessed vs predicted}}$
Training group	1690 ± 447	2542 ± 355	67	< 0.001
Control group	1763 ± 362	2497 ± 396	71	< 0.001

OUES: oxygen uptake efficiency slope (constant a in equation $\dot{V}O_2 = a \cdot \log \dot{V}E + b$).

(Greenhouse–Geisser P value was 0.09), there was no need to correct for multiple comparisons. Exercise training increased OUES75 significantly by 21% and OUES90 by 22%. Again there was no significant change in the control group (Table 2).

OUES assessed in the control group and in the training group were significantly lower (71 and 67%, respectively) than reference OUES values for matched normal participants (Table 3).

New York Heart Association functional class

Baseline NYHA functional class of the training and the control groups did not differ significantly. After the exercise training program, 10 patients improved one NYHA functional class, and one patient improved two NYHA functional classes ($P < 0.01$).

Discussion

As compared with normal values, baseline $\dot{V}_{O_{2peak}}$ and OUES were depressed, baseline $\dot{V}E/\dot{V}_{CO_2}$ slope was increased. According to expectation [13], exercise training increased $\dot{V}_{O_{2peak}}$ and decreased $\dot{V}E/\dot{V}_{CO_2}$ slope. The control group showed an increasing trend of OUES, probably caused by a familiarization effect. Nevertheless, the increase of OUES in the exercise group differed significantly from the change in the control group. Therefore, our study confirmed our hypothesis that exercise training increases OUES in CHF patients. To our knowledge, this is the first controlled study that reports a beneficial effect of exercise training on OUES in CHF. This finding is of great potential interest. Multiple factors affect the maximal load attained during a symptom-limited maximal exercise test [5,6]. As a consequence, individual $\dot{V}_{O_{2peak}}$ values are relatively unreliable. Contrastingly, we found, in line with the findings by Hollenberg *et al.* [9] and van Laethem *et al.* [10], that OUES is a more consistent parameter. Hence, OUES75 and OUES90 also increased significantly in the exercise training group.

Physiological background of oxygen uptake efficiency slope

OUES was significantly lower than the computed OUES reference values. Factors affecting OUES are the arterial carbon dioxide set point (P_aCO_2), the metabolic carbon dioxide production ($\dot{V}_{CO_2}$) and the ratio of pulmonary dead space to tidal volume (Vd/Vt) [7]. During exercise, the arterial carbon dioxide set point in CHF patients does not differ from normal [20]. Metabolic acidosis in CHF patients, however, occurs at lower work loads than in healthy persons as a consequence of reduced muscle perfusion and structural muscular changes [21]. This causes increased ventilation [21]. Moreover, the reduced lung perfusion in CHF patients results in an increase in the physiologic pulmonary dead space [7]. Hence, a depressed OUES in CHF patients is likely resulting from underperfusion of skeletal muscle and underperfusion of the lungs. The observed exercise training-induced increase in OUES is therefore presumably attributable to both peripheral muscular adaptations, such as increased capillary density, blood flow, mitochondrial volume density, fibre size, slow twitch fibres and decreased lactic acidosis and vascular resistance [22–25], and pulmonary adaptations such as increased alveolar capillary membrane perfusion and capillary blood flow [14]. In accordance with this, the decrease in $\dot{V}E/\dot{V}_{CO_2}$ slope indicates decreased lactic acidosis and a better ventilation/perfusion match in the lungs.

Limitations

Although our study was not randomized, the baseline characteristics of the control and exercise groups matched reasonably well (Table 1). Moreover, although the duration between the two exercise tests in the control group is probably not of great importance, it is a limitation that there was a discrepancy in the time between the initial and the second exercise test between the two groups.

Whether similar results (more specifically, a significant increase of OUES in the training group) would have been obtained with other exercise training modalities

(e.g. walking/running instead of endurance cycling) or with other exercise testing modalities (e.g. treadmill vs. cycle ergometry) cannot be answered with our current data. So far, standard exercise testing protocol has been defined for OUES assessment, and OUES is currently being measured with treadmill as well as with cycle ergometry [7,8,10,11,15]. Baba *et al.* [26] have shown that there was excellent intraindividual agreement between OUES values measured with two different treadmill protocols. Hence, OUES seems to be relatively insensitive to the testing protocol, and it is not very likely that the results of our study would have differed very much when treadmill instead of cycle ergometry had been used.

Conclusion

In conclusion, our study demonstrates that exercise training in CHF patients increases OUES, a robust parameter for cardiorespiratory reserve with a strong independent prognostic value in heart failure. This positive training effect is associated with an improvement in the NYHA functional class and other cardiorespiratory parameters. Follow-up studies are needed to determine whether an increase of OUES in a heart failure patient is associated with improved prognosis.

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References

1 Taylor HL, Buskirk E, Henschel A. Maximal oxygen intake as an objective measure of cardio-respiratory performance. *J Appl Physiol* 1955; **8**: 73–80.
2 Myers J, Walsh D, Buchanan N, Froelicher VF. Can maximal cardiopulmonary capacity be recognized by a plateau in oxygen uptake? *Chest* 1989; **96**:1312–1316.
3 Swedberg K, Gundersen T. The role of exercise testing in heart failure. *J Cardiovasc Pharmacol* 1993; **22**(**Suppl 9**):S13–S17.
4 Piepoli MF, Corra U, Agostoni PG, Belardinelli R, Cohen-Solal A, Hambrecht R, *et al.* Statement on cardiopulmonary exercise testing in chronic heart failure due to left ventricular dysfunction: recommendations for performance and interpretation. Part I: definition of cardiopulmonary exercise testing parameters for appropriate use in chronic heart failure. *Eur J Cardiovasc Prev Rehabil* 2006; **13**:150–164.
5 Andreacci JL, LeMura LM, Cohen SL, Urbansky EA, Chelland SA, Von Duvillard SP. The effects of frequency of encouragement on performance during maximal exercise testing. *J Sports Sci* 2002; **20**:345–352.
6 St Clair GA, Lambert MI, Hawley JA, Broomhead SA, Noakes TD. Measurement of maximal oxygen uptake from two different laboratory protocols in runners and squash players. *Med Sci Sports Exerc* 1999; **31**:1226–1229.
7 Baba R, Nagashima M, Goto M, Nagano Y, Yokota M, Tauchi N, *et al.* Oxygen uptake efficiency slope: a new index of cardiorespiratory functional reserve derived from the relation between oxygen uptake and minute ventilation during incremental exercise. *J Am Coll Cardiol* 1996; **28**: 1567–1572.
8 Baba R, Tsuyuki K, Kimura Y, Ninomiya K, Aihara M, Ebine K, *et al.* Oxygen uptake efficiency slope as a useful measure of cardiorespiratory functional reserve in adult cardiac patients. *Eur J Appl Physiol Occup Physiol* 1999; **80**:397–401.
9 Hollenberg M, Tager IB. Oxygen uptake efficiency slope: an index of exercise performance and cardiopulmonary reserve requiring only submaximal exercise. *J Am Coll Cardiol* 2000; **36**:194–201.
10 Van Laethem C, Bartunek J, Goethals M, Nellens P, Andries E, Vanderheyden M. Oxygen uptake efficiency slope, a new submaximal parameter in evaluating exercise capacity in chronic heart failure patients. *Am Heart J* 2005; **149**:175–180.
11 Davies LC, Wensel R, Georgiadou P, Cicoira M, Coats AJ, Piepoli MF, *et al.* Enhanced prognostic value from cardiopulmonary exercise testing in chronic heart failure by non-linear analysis: oxygen uptake efficiency slope. *Eur Heart J* 2006; **27**:684–690.
12 Roditis P, Dimopoulos S, Sakellariou D, Sarafoglou S, Kaldara E, Venetsanakos J, *et al.* The effects of exercise training on the kinetics of oxygen uptake in patients with chronic heart failure. *Eur J Cardiovasc Prev Rehabil* 2007; **14**:304–311.
13 Rees K, Taylor RS, Singh S, Coats AJ, Ebrahim S. Exercise based rehabilitation for heart failure. *Cochrane Database Syst Rev* 2004;CD003331.
14 Guazzi M, Reina G, Tumminello G, Guazzi MD. Improvement of alveolar-capillary membrane diffusing capacity with exercise training in chronic heart failure. *J Appl Physiol* 2004; **97**:1866–1873.
15 Defoor J, Schepers D, Reybrouck T, Fagard R, Vanhees L. Oxygen uptake efficiency slope in coronary artery disease: clinical use and response to training. *Int J Sports Med* 2006; **27**:730–737.
16 Tsuyuki K, Kimura Y, Chiashi K, Matsushita C, Ninomiya K, Choh K, *et al.* Oxygen uptake efficiency slope as monitoring tool for physical training in chronic hemodialysis patients. *Ther Apher Dial* 2003; **7**: 461–467.
17 Van Laethem C, Van De Veire NV, Backer GD, Bihija S, Seghers T, Cambier D, *et al.* Response of the oxygen uptake efficiency slope to exercise training in patients with chronic heart failure. *Eur J Heart Fail* 2007; **9**: 625–629.
18 Rickham PP. Human Experimentation. Code of ethics of the World Medical Association. Declaration of Helsinki. *Br Med J* 1964; **2**:177.
19 Buller NP, Poole-Wilson PA. Mechanism of the increased ventilatory response to exercise in patients with chronic heart failure. *Br Heart J* 1990; **63**:281–283.
20 Sullivan MJ, Cobb FR. The anaerobic threshold in chronic heart failure. Relation to blood lactate, ventilatory basis, reproducibility, and response to exercise training. *Circulation* 1990; **81**(**1 Suppl**):II47–II58.
21 Pina IL, Apstein CS, Balady GJ, Belardinelli R, Chaitman BR, Duscha BD, *et al.* Exercise and heart failure: a statement from the American Heart Association Committee on exercise, rehabilitation, and prevention. *Circulation* 2003; **107**:1210–1225.
22 Hambrecht R, Gielen S, Linke A, Fiehn E, Yu J, Walther C, *et al.* Effects of exercise training on left ventricular function and peripheral resistance in patients with chronic heart failure: a randomized trial. *JAMA* 2000; **283**:3095–3101.
23 Hambrecht R, Fiehn E, Yu J, Niebauer J, Weigl C, Hilbrich L, *et al.* Effects of endurance training on mitochondrial ultrastructure and fiber type distribution in skeletal muscle of patients with stable chronic heart failure. *J Am Coll Cardiol* 1997; **29**:1067–1073.
24 Gordon A, Tyni-Lenne R, Persson H, Kaijser L, Hultman E, Sylven C. Markedly improved skeletal muscle function with local muscle training in patients with chronic heart failure. *Clin Cardiol* 1996; **19**:568–574.
25 Piepoli MF, Scott AC, Capucci A, Coats AJ. Skeletal muscle training in chronic heart failure. *Acta Physiol Scand* 2001; **171**:295–303.
26 Baba R, Nagashima M, Nagano Y, Ikoma M, Nishibata K. Role of the oxygen uptake efficiency slope in evaluating exercise tolerance. *Arch Dis Child* 1999; **81**:73–75.